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(54) Title: SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR TREATMENT OF MEDICAL DISORDERS

(57) Abstract: The invention pertains to methods and compositions for treating medical disorders characterized by elevated levels or abnormal expression of TNF $\alpha$  by administering a TNF $\alpha$  inhibitor, such as recombinant TNFR:Fc, and to combination treatments involving the administration of a TNF $\alpha$  inhibitor and an IL-4 inhibitor. Also provided are methods and compositions involving IL-4 inhibitors for use in treating neurological disorders.

## SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR TREATMENT OF MEDICAL DISORDERS

10        This application is a continuation-in-part of United States patent application 09/726,781, filed November 29, 2000, which is a continuation-in-part of 09/602,351, filed June 23, 2000, which is a continuation-in-part of PCT/US00/10565, filed April 19, 2000, (claiming the benefit of priority from United States provisional applications 60/184,864, filed February 25, 2000, and 60/164,676, filed November 10, 1999), which is a continuation-in-part of 09/373,828, filed 15        August 13, 1999 (claiming the benefit of priority from United States provisional applications 60/148,234, filed August 11, 1999; 60/143,959, filed July 15, 1999; 60/134,320, filed May 14, 1999; and 60/130,074, filed April 19, 1999).

### FIELD OF THE INVENTION

20        The invention pertains to methods for treating various medical disorders that are characterized by abnormal or excessive TNF $\alpha$  levels by administering a TNF $\alpha$  antagonist, preferably a soluble TNF $\alpha$ . The TNF $\alpha$  inhibitor may be administered in combination with other biologically active molecules, such as IL-4 inhibitors. Also provided are methods and compositions involving IL-4 inhibitors for use in treating neurological disorders.

### BACKGROUND OF THE INVENTION

25        The pleiotropic cytokine tumor necrosis factor alpha (TNF $\alpha$ ) is associated with inflammation and binds to cells through membrane receptor molecules, including two molecules having molecular weights of approximately 55 kDa and 75 kDa (p55 and p75). In addition to binding TNF $\alpha$ , the p55 and p75 TNF receptors mediate the binding to cells of homotrimers of TNF $\beta$ , which is another cytokine associated with inflammation and which shares structural 30        similarities with TNF $\alpha$  (e.g., see Cosman, *Blood Cell Biochem* 7:51-77, 1996). TNF $\beta$  is also known as lymphotoxin- $\alpha$  (LT $\alpha$ ).

35        It has been proposed that a systemic or localized excess of TNF $\alpha$  contributes to the progression of numerous medical disorders. For example, patients with chronic heart failure have elevated levels of serum TNF $\alpha$ , which have been shown to increase with disease progression (see, for example, Levine et al., *N Eng J Med* 323:236-241, 1990). A variety of other diseases are associated with elevated levels of TNF $\alpha$  (see, for example, Feldman et al., *Transplantation Proceedings* 30:4126-4127, 1998).

5 It has been suggested that the suppression of TNF $\alpha$  might be beneficial in patients suffering from various disorders characterized by abnormal or excessive TNF $\alpha$  expression. However, although progress has been made in devising effective treatment for such diseases, improved medicaments and methods of treatment are needed.

### SUMMARY OF THE INVENTION

10 Provided herein are methods for treating a number of medical disorders characterized by abnormal TNF $\alpha$  expression by repeatedly administering an antagonist of TNF $\alpha$ , such as a soluble TNF $\alpha$  receptor, for a period of time sufficient to induce a sustained improvement in the patient's condition. TNF $\alpha$  inhibitors may be administered in combination with other biologically active molecules, such as IL-4 inhibitors or inhibitors of other proinflammatory cytokines.

### DETAILED DESCRIPTION OF THE INVENTION

15 This invention provides compounds, compositions and methods for treating a mammalian patient, including a human patient, who is suffering from a medical disorder that is characterized by abnormal or elevated expression of TNF $\alpha$ . For purposes of this disclosure, the terms "illness," "disease," "medical condition," "abnormal condition" and the like are used interchangeably with 20 the term "medical disorder."

The subject methods involve administering to the patient a soluble TNF $\alpha$  antagonist that is capable of reducing the effective amount of endogenous biologically active TNF $\alpha$ , such as by reducing the amount of TNF $\alpha$  produced, or by preventing the binding of TNF $\alpha$  to its cell surface receptor (TNFR). Antagonists capable of inhibiting this binding include receptor-binding peptide fragments of TNF $\alpha$ , antisense oligonucleotides or ribozymes that inhibit TNF $\alpha$  production, antibodies directed against TNF $\alpha$ , and recombinant proteins comprising all or portions of receptors for TNF $\alpha$  or modified variants thereof, including genetically-modified muteins, multimeric forms and sustained-release formulations. In other embodiments of the invention, the diseases discussed herein are treated with molecules that inhibit the formation of the IgA- $\alpha_1$ AT complex, such as the peptides disclosed in EP 0 614 464 B, or antibodies against this complex. The herein-described conditions also may be treated with disaccharides, sulfated derivatives of glucosamine or other similar carbohydrates as described in U.S. 6,020,323. In addition, the herein-described diseases may be treated with the peptide TNF $\alpha$  inhibitors disclosed in U.S. 5,641,751 and U.S. 5,519,000, and the D-amino acid-containing peptides described in 30 U.S. 5,753,628. In addition, the conditions described herein may be treated with inhibitors of 35 TNF $\alpha$  converting enzyme.

5 Other compounds suitable for treating the diseases described herein include small molecules such as thalidomide or thalidomide analogs, pentoxifylline, or matrix metalloproteinase (MMP) inhibitors or other small molecules. Suitable MMP inhibitors include, for example, those described in U.S. Patent Nos. 5,883,131, 5,863,949 and 5,861,510 as well as the mercapto alkyl peptidyl compounds described in U.S. 5,872,146. Other small molecules  
10 capable of reducing TNF $\alpha$  production, include, for example, the molecules described in U.S. Patent Nos. 5,508,300, 5,596,013 and 5,563,143, any of which can be administered in combination with TNF $\alpha$  inhibitors such as soluble TNFRs or antibodies against TNF $\alpha$ . Additional small molecules useful for treating the TNF $\alpha$ -mediated diseases described herein include the MMP inhibitors that are described in U.S. 5,747,514, U.S. 5,691,382, as well as the  
15 hydroxamic acid derivatives described in U.S. 5,821,262. The diseases described herein also may be treated with small molecules that inhibit phosphodiesterase IV and TNF $\alpha$  production, such as substituted oxime derivatives (WO 96/00215), quinoline sulfonamides (U.S. 5,834,485), aryl furan derivatives (WO 99/18095) and heterobicyclic derivatives (WO 96/01825; GB 2 291 422 A). Also useful are thiazole derivatives that suppress TNF $\alpha$  and IFN $\gamma$   
20 (WO 99/15524), as well as xanthine derivatives that suppress TNF $\alpha$  and other proinflammatory cytokines (see, for example, U.S. 5,118,500, U.S. 5,096,906 and U.S. 5,196,430). Additional small molecules useful for treating the herein-described conditions include those disclosed in U.S. 5,547,979.

Also included among the TNF $\alpha$  inhibitors of the invention are antisense oligonucleotides  
25 that act to directly block the translation of mRNA by hybridizing to targeted mRNA and preventing polypeptide translation. Antisense oligonucleotides are suitable for use in treating any of the medical disorders disclosed herein, either alone or in combination with other TNF $\alpha$  inhibitors, such as TNFR:Fc, or in combination with other agents for treating the same condition. Antisense molecules of the invention may interfere with the translation of TNF $\alpha$ , a TNF $\alpha$   
30 receptor, or an enzyme in the metabolic pathways for the synthesis of TNF $\alpha$ . Absolute complementarity, although preferred, is not required. A sequence "complementary" to a portion of a nucleic acid, as referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the nucleic acid, forming a stable duplex (or triplex, as appropriate). The ability to hybridize will depend on both the degree of complementarity and the length of the  
35 antisense nucleic acid. Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, oligonucleotides complementary to either the 5'- or 3'- non-translated, non-coding regions of the targeted transcript can be used.

5 Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon.

Antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 10 50 nucleotides. Most preferably, they will contain 18-21 nucleotides.

The backbone of antisense oligonucleotides may be chemically modified to prolong the half-life of the oligonucleotide in the body. Suitable modifications for this purpose are known in the art, such as those disclosed, for example, in U.S. Patent No. 6,114,517, which describes the use for this purpose of phosphorothioates, phosphorodithioates, phosphotriesters, 15 aminoalkylphosphotriesters, methyl and other alkyl phosphonates, various phosphonates, phosphinates, and phosphoramidates and so on.

The oligonucleotides can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve 20 stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, e.g., Letsinger *et al.*, 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556; Lemaitre *et al.*, 1987, Proc. Natl. Acad. Sci. 84:648-652; PCT Publication No. WO88/09810, published Dec. 15, 1988), or hybridization-triggered cleavage agents or 25 intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5:539-549). The antisense molecules should be delivered to cells which express the targeted transcript.

Antisense oligonucleotides can be administered parenterally, including by intravenous or subcutaneous injection, or they can be incorporated into formulations suitable for oral administration, such as, for example, ISIS 104838, which targets TNF $\alpha$ . A number of methods 30 have been developed for delivering antisense DNA or RNA to cells; e.g., antisense molecules can be injected directly into the tissue or cell derivation site, or modified antisense molecules, designed to target the desired cells (e.g., antisense linked to peptides or antibodies that specifically bind receptors or antigens expressed on the target cell surface) can be administered systemically. However, it is often difficult to achieve intracellular concentrations of the antisense 35 sufficient to suppress translation of endogenous mRNAs. Therefore a preferred approach utilizes a recombinant DNA construct in which the antisense oligonucleotide is placed under the control of a strong pol III or pol II promoter. The use of such a construct to transfect target cells in the patient will result in the transcription of sufficient amounts of single stranded RNAs that will

5 form complementary base pairs with the endogenous target gene transcripts and thereby prevent translation of the targeted mRNA. For example, a vector can be introduced *in vivo* such that it is taken up by a cell and directs the transcription of an antisense RNA. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology

10 methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in mammalian cells. Antisense oligonucleotides for suitable for treating diseases associated with elevated TNF $\alpha$  include, for example, the anti-TNF $\alpha$  oligonucleotides described in U.S. Patent No. 6,080,580, which proposes the use of such oligonucleotides as candidates for testing in animal models of diabetes mellitus, rheumatoid

15 arthritis, contact sensitivity, Crohn's disease, multiple sclerosis, pancreatitis, hepatitis and heart transplant.

Ribozyme molecules designed to catalytically cleave mRNA transcripts can also be used to prevent the translation of mRNAs encoding TNF $\alpha$ , TNF $\alpha$  receptors, or enzymes involved in synthesis of TNF $\alpha$  or TNFRs (see, *e.g.*, PCT WO90/11364; US Patent No. 5,824,519).

20 Ribozymes useful for this purpose include hammerhead ribozymes (Haseloff and Gerlach, 1988, *Nature*, 334:585-591), RNA endoribonucleases (hereinafter "Cech-type ribozymes") such as the one that occurs naturally in *Tetrahymena thermophila* (known as the IVS, or L-19 IVS RNA) (see, for example, WO 88/04300; Been and Cech, 1986, *Cell*, 47:207-216). Ribozymes can be composed of modified oligonucleotides (*e.g.* for improved stability, targeting, etc.) and should be

25 delivered to cells which express the target peptide *in vivo*. A preferred method of delivery involves using a DNA construct encoding the ribozyme under the control of a strong constitutive pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous target mRNA, thereby inhibiting its translation.

Alternatively, expression of genes involved in TNF $\alpha$  or TNFR production can be reduced

30 by targeting deoxyribonucleotide sequences complementary to the regulatory region of the target gene (*i.e.*, the target gene promoter and/or enhancers) to form triple helical structures that prevent transcription of the target gene. (see, for example, Helene, 1991, *Anticancer Drug Des.*, 6(6), 569-584; Helene, et al., 1992, *Ann. N.Y. Acad. Sci.*, 660, 27-36; and Maher, 1992, *Bioassays* 14(12), 807-815).

35 Anti-sense RNA and DNA, ribozyme, and triple helix molecules of the invention may be prepared by any method known in the art for the synthesis of DNA and RNA molecules, including, for example, solid phase phosphoramidite chemical synthesis. Oligonucleotides can be synthesized by standard methods known in the art, *e.g.* by use of an automated DNA synthesizer

5 (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein *et al.*, 1988, Nucl. Acids Res. 16:3209, and methylphosphonate oligonucleotides can be prepared as described by Sarin *et al.*, 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451. Alternatively, RNA molecules may be generated by *in vitro* and *in vivo* transcription of DNA sequences encoding the antisense 10 RNA molecule. Such DNA sequences may be incorporated into a wide variety of vectors that incorporate suitable RNA polymerase promoters such as the T7 or SP6 polymerase promoters. Alternatively, antisense cDNA constructs that synthesize antisense RNA constitutively or inducibly, depending on the promoter used, can be introduced stably into cell lines.

15 Endogenous target gene expression can also be reduced by inactivating or "knocking out" the target gene or its promoter using targeted homologous recombination (e.g., see Smithies, et al., 1985, Nature 317, 230-234; Thomas and Capecchi, 1987, Cell 51, 503-512; Thompson, et al., 1989, Cell 5, 313-321). For example, a mutant, non-functional target gene (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous target gene (either the coding regions or regulatory regions of the target gene) can be used, with or without a selectable 20 marker and/or a negative selectable marker, to transfet cells that express the target gene *in vivo*. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the target gene. Such approaches are particularly suited in the agricultural field where modifications to ES (embryonic stem) cells can be used to generate animal offspring with an inactive target gene (e.g., see Thomas and Capecchi, 1987 and Thompson, 1989, *supra*), or in 25 model organisms such as *Caenorhabditis elegans* where the "RNA interference" ("RNAi") technique (Grishok A, Tabara H, and Mello CC, 2000, *Science* 287 (5462): 2494-2497), or the introduction of transgenes (Dernburg et al., 2000, *Genes Dev.* 14 (13): 1578-1583) are used to inhibit the expression of specific target genes. This approach can be adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required 30 site *in vivo* using appropriate vectors such as viral vectors.

Preferred embodiments of the invention utilize soluble TNFRs as the TNF $\alpha$  antagonist. Soluble forms of TNFRs may include monomers, fusion proteins (also called "chimeric proteins"), dimers, trimers or higher order multimers. In certain embodiments of the invention, the soluble TNFR derivative is one that mimics the 75 kDa TNFR or the 55 kDa TNFR and that binds to 35 TNF $\alpha$  in the patient's body. The soluble TNFR mimics of the present invention may be derived from TNFRs p55 or p75 or fragments thereof. TNFRs other than p55 and p75 also are useful for deriving soluble compounds for treating the various medical disorders described herein, such for example the TNFR that is described in WO 99/04001. Soluble TNFR molecules used to

5 construct TNFR mimics include, for example, analogs or fragments of native TNFRs having at least 20 amino acids; that lack the transmembrane region of the native TNFR, and that are capable of binding TNF $\alpha$ . Antagonists derived from TNFRs compete for TNF $\alpha$  with the receptors on the cell surface, thus inhibiting TNF $\alpha$  from binding to cells, thereby preventing it from manifesting its biological activities. Binding of soluble TNFRs to TNF $\alpha$  or LT $\alpha$  can be  
10 assayed using ELISA or any other convenient assay. This invention provides for the use of soluble TNF $\alpha$  receptors in the manufacture of medicaments for the treatment of numerous diseases.

The soluble TNFR polypeptides or fragments of the invention may be fused with a second polypeptide to form a chimeric protein. The second polypeptide may promote the  
15 spontaneous formation by the chimeric protein of a dimer, trimer or higher order multimer that is capable of binding a TNF $\alpha$  or a LT $\alpha$  molecule and preventing it from binding to cell-bound receptors. Chimeric proteins used as antagonists include, for example, molecules derived from the constant region of an antibody molecule and the extracellular portion of a TNFR. Such molecules are referred to herein as TNFR-Ig fusion proteins. A preferred TNFR-Ig fusion protein  
20 suitable for treating diseases in humans and other mammals is recombinant TNFR:Fc, a term which as used herein refers to "etanercept," which is a dimer of two molecules of the extracellular portion of the p75 TNF $\alpha$  receptor, each molecule consisting of a 235 amino acid TNFR-derived polypeptide that is fused to a 232 amino acid Fc portion of human IgG<sub>1</sub>. Etanercept is currently sold by Immunex Corporation under the trade name ENBREL.<sup>®</sup> Because the p75 receptor protein  
25 that it incorporates binds not only to TNF $\alpha$ , but also to the inflammatory cytokine LT $\alpha$ , etanercept can act as a competitive inhibitor not only of TNF $\alpha$ , but also of LT $\alpha$ . This is in contrast to antibodies directed against TNF $\alpha$ , which cannot inhibit LT $\alpha$ . Also encompassed by the invention are treatments using a compound that comprises the extracellular portion of the 55 kDa TNFR fused to the Fc portion of IgG, as well as compositions and combinations containing  
30 such a molecule. Encompassed also are therapeutic methods involving the administration of soluble TNFRs derived from the extracellular regions of TNF $\alpha$  receptor molecules other than the p55 and p75 TNFRs, such as for example the TNFR described in WO 99/04001, including TNFR-Id's derived from this TNFR. Other suitable TNF $\alpha$  inhibitors include the humanized anti-TNF $\alpha$  antibody D2E7 (Knoll Pharmaceutical/BASF AG).

35 In one preferred embodiment of the invention, sustained-release forms of soluble TNFRs are used, including sustained-release forms of TNFR:Fc. Sustained-release forms suitable for use in the disclosed methods include, but are not limited to, TNFRs that are encapsulated in a slowly-

5 dissolving biocompatible polymer (such as the alginate microparticles described in U.S. 6,036,978 or the polyethylene-vinyl acetate and poly(lactic-glucolic acid) compositions described in U.S. 6,083,534), admixed with such a polymer (including topically applied hydrogels), and or encased in a biocompatible semi-permeable implant. In addition, a soluble TNFR type I or type II for use in the hereindescribed therapies may be conjugated with  
10 polyethylene glycol (pegylated) to prolong its serum half-life or to enhance protein delivery.

In accord with this invention, medical disorders characterized by abnormal or excess expression of TNF $\alpha$  are administered a therapeutically effective amount of a TNF $\alpha$  inhibitor. The TNF $\alpha$  inhibitor may be a TNF $\alpha$ -binding soluble TNF $\alpha$  receptor, preferably TNFR:Fc. As used herein, the phrase "administering a therapeutically effective amount" of a therapeutic agent  
15 means that the patient is treated with the agent in an amount and for a time sufficient to induce a sustained improvement over baseline in at least one indicator that reflects the severity of the disorder. An improvement is considered "sustained" if the patient exhibits the improvement on at least two occasions separated by one or more weeks. The degree of improvement is determined based on signs or symptoms, and determinations may also employ questionnaires that are  
20 administered to the patient, such as quality-of-life questionnaires.

Various indicators that reflect the extent of the patient's illness may be assessed for determining whether the amount and time of the treatment is sufficient. The baseline value for the chosen indicator or indicators is established by examination of the patient prior to administration of the first dose of the etanercept or other TNF $\alpha$  inhibitor. Preferably, the baseline  
25 examination is done within about 60 days of administering the first dose. If the TNF $\alpha$  antagonist is being administered to treat acute symptoms, such as for example to treat a traumatic knee injury, the first dose is administered as soon as practically possible after the injury has occurred.

Improvement is induced by administering TNFR:Fc or other TNF $\alpha$  antagonist until the patient manifests an improvement over baseline for the chosen indicator or indicators. In treating  
30 chronic conditions, this degree of improvement is obtained by repeatedly administering this medicament over a period of at least a month or more, e.g., for one, two, or three months or longer, or indefinitely. A period of one to six weeks, or even a single dose, often is sufficient for treating acute conditions. For injuries or acute conditions, a single dose may be sufficient.

Although the extent of the patient's illness after treatment may appear improved  
35 according to one or more indicators, treatment may be continued indefinitely at the same level or at a reduced dose or frequency. Once treatment has been reduced or discontinued, it later may be resumed at the original level if symptoms should reappear.

5 Any efficacious route of administration may be used to therapeutically administer TNFR:Fc or other TNF $\alpha$  antagonists. If injected, TNFR:Fc can be administered, for example, via intra-articular, intravenous, intramuscular, intralesional, intraperitoneal or subcutaneous routes by bolus injection or by continuous infusion. Other suitable means of administration include sustained release from implants, aerosol inhalation, eyedrops, oral preparations, including pills, 10 syrups, lozenges or chewing gum, and topical preparations such as lotions, gels, sprays, ointments or other suitable techniques. Alternatively, proteinaceous TNF $\alpha$  inhibitors, such as a soluble TNFR, may be administered by implanting cultured cells that express the protein, for example, by implanting cells that express TNFR:Fc. In one embodiment, the patient's own cells are induced 15 to produce TNFR:Fc by transfection *in vivo* or *ex vivo* with a DNA that encodes TNFR:Fc. This DNA can be introduced into the patient's cells, for example, by injecting naked DNA or liposome-encapsulated DNA that encodes TNFR:Fc, by infection with a viral vector expressing the DNA, or by other means known in the art. When TNFR:Fc is administered in combination with one or more other biologically active compounds, these may be administered by the same or by different routes, and may be administered simultaneously, separately or sequentially.

20 TNFR:Fc or other soluble TNFRs or other TNF inhibitors preferably are administered in the form of a physiologically acceptable composition comprising purified recombinant protein in conjunction with physiologically acceptable carriers, excipients or diluents. Such carriers are nontoxic to recipients at the dosages and concentrations employed. Ordinarily, the preparation of such compositions entails combining the TNF $\alpha$  antagonist with buffers, antioxidants such as 25 ascorbic acid, low molecular weight polypeptides (such as those having fewer than 10 amino acids), proteins, amino acids, carbohydrates such as glucose, sucrose or dextrans, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with conspecific serum albumin are exemplary appropriate diluents. In accordance with appropriate industry standards, preservatives may also be added, such as benzyl alcohol. 30 TNFR:Fc preferably is formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents. Suitable components are nontoxic to recipients at the dosages and concentrations employed. Further examples of components that may be employed in pharmaceutical formulations are presented in *Remington's Pharmaceutical Sciences*, 16<sup>th</sup> Ed., Mack Publishing Company, Easton, PA, 1980.

35 Appropriate dosages can be determined in standard dosing trials, and may vary according to the chosen route of administration. The amount and frequency of administration will depend on such factors as the nature and severity of the indication being treated, the desired response, the age and condition of the patient, and so forth.

5        In one embodiment of the invention, TNFR:Fc is administered one time per week to treat the various medical disorders disclosed herein, in another embodiment is administered at least two times per week, and in another embodiment is administered at least three times per week. An adult patient is a person who is 18 years of age or older. If injected, the effective amount of TNFR:Fc per adult dose ranges from 1-20 mg/m<sup>2</sup>, and preferably is about 5-12 mg/m<sup>2</sup>.

10      Alternatively, a flat dose may be administered, whose amount may range from 5-100 mg/dose. Exemplary dose ranges for a flat dose to be administered by subcutaneous injection are 5-25 mg/dose, 25-50 mg/dose and 50-100 mg/dose. In one embodiment of the invention, the various indications described below are treated by administering a preparation acceptable for injection containing TNFR:Fc at 25 mg/dose, or alternatively, containing 50 mg per dose. The

15      25 mg or 50 mg dose may be administered repeatedly, particularly for chronic conditions. If a route of administration other than injection is used, the dose is appropriately adjusted in accord with standard medical practices. In many instances, an improvement in a patient's condition will be obtained by injecting a dose of about 25 mg of TNFR:Fc one to three times per week over a period of at least three weeks, or a dose of 50 mg of TNFR:Fc one or two times per week for at

20      least three weeks, though treatment for longer periods may be necessary to induce the desired degree of improvement. For incurable chronic conditions, the regimen may be continued indefinitely, with adjustments being made to dose and frequency if such are deemed necessary by the patient's physician.

For pediatric patients (age 4-17), a suitable regimen involves the subcutaneous injection of 0.4 mg/kg, up to a maximum dose of 25 mg of TNFR:Fc, administered by subcutaneous injection one or more times per week.

The invention further includes the administration of a soluble TNFR, such as TNFR:Fc, concurrently with one or more other drugs that are administered to the same patient in combination with the soluble TNFR, each drug being administered according to a regimen suitable for that medicament. "Concurrent administration" encompasses simultaneous or sequential treatment with the components of the combination, as well as regimens in which the drugs are alternated, or wherein one component is administered long-term and the other(s) are administered intermittently. Components may be administered in the same or in separate compositions, and by the same or different routes of administration. Examples of drugs to be administered concurrently include but are not limited to antivirals, antibiotics, analgesics, corticosteroids, antagonists of inflammatory cytokines, DMARDs and non-steroidal anti-inflammatories. DMARDs that can be administered in combination with the subject TNF $\alpha$  inhibitors such as TNFR:Fc include azathioprine, cyclophosphamide, cyclosporine,

5 hydroxychloroquine sulfate, methotrexate, leflunomide, minocycline, penicillamine, sulfasalazine and gold compounds such as oral gold, gold sodium thiomalate and aurothioglucose. Additionally, TNFR:Fc may be combined with a second TNF $\alpha$  antagonist, including an antibody 10 against TNF $\alpha$  or TNFR, a TNF $\alpha$ -derived peptide that acts as a competitive inhibitor of TNF $\alpha$  (such as those described in U.S. 5,795,859 or U.S. 6,107,273), a TNFR-IgG fusion protein other than etanercept, such as one containing the extracellular portion of the p55 TNF $\alpha$  receptor, a soluble TNFR other than an IgG fusion protein, or other molecules that reduce endogenous TNF $\alpha$  levels, such as inhibitors of the TNF $\alpha$  converting enzyme (see e.g., U.S. 5,594,106), or any of the small molecules or TNF $\alpha$  inhibitors that are described above, including pentoxifylline or thalidomide.

15 If an antibody against TNF $\alpha$  is used as the TNF $\alpha$  inhibitor, a preferred dose range is 0.1 to 20 mg/kg, and more preferably is 1-10 mg/kg. Another preferred dose range for anti-TNF $\alpha$  antibody is 0.75 to 7.5 mg/kg of body weight. Humanized antibodies are preferred, that is, antibodies in which only the antigen-binding portion of the antibody molecule is derived from a non-human source. An exemplary humanized antibody for treating the herein-described diseases 20 is infliximab (sold by Centocor as REMICADE $^{\circledR}$ ), which is a chimeric IgG1 $\kappa$  monoclonal antibody having an approximate molecular weight of 149,100 daltons. Infliximab is composed of human constant and murine variable regions, and binds specifically to human TNF $\alpha$ . Other suitable anti-TNF $\alpha$  antibodies include the humanized antibodies D2E7 and CDP571, and the antibodies described in EP 0 516 785 B1, U.S. 5,656,272, EP 0 492 448 A1. Such antibodies 25 may be injected or administered intravenously.

In one preferred embodiment of the invention, the various medical disorders disclosed herein as being treatable with inhibitors of TNF $\alpha$  are treated in combination with another cytokine or cytokine inhibitor. For example, a soluble TNFR such as TNFR:Fc may be administered in a composition that also contains a compound that inhibits the interaction of other 30 inflammatory cytokines with their receptors. Examples of cytokine inhibitors used in combination with TNFR:Fc include, for example, antagonists of TGF $\beta$ , IL-6 or IL-8. TNF $\alpha$  inhibitors such as TNFR:Fc also may be administered in combination with the cytokines GM-CSF, IL-2 and inhibitors of protein kinase A type 1 to enhance T cell proliferation in HIV-infected patients who are receiving anti-retroviral therapy. In addition, TNF $\alpha$  inhibitors may be 35 combined with inhibitors of IL-13 to treat Hodgkin's disease.

Other combinations for treating the herein-described diseases include TNFR:Fc administered concurrently with compounds that block the binding of RANK and RANK-ligand,

5 such as antagonistic antibodies against RANK or RANK-ligand, osteoprotegerin or soluble forms of RANK, including RANK:Fc, and soluble forms of RANK-ligand that do not trigger RANK. Soluble forms of RANK suitable for these combinations are described, for example, in U.S. 6,017,729. Other RANK antagonists suitable for use in the described combinations include antisense oligonucleotides, such as those described in U.S. Patent No. 6,171,860. The concurrent  
10 administration of TNFR:Fc together with RANK:Fc, osteoprotegerin or another RANK antagonist is useful for preventing bone destruction in various settings including but not limited to osteoporosis, multiple myeloma or other malignancies that cause bone degeneration, or anti-tumor therapy aimed at preventing metastasis to bone, or bone destruction associated with prosthesis wear debris or with periodontitis. Tumors that are treatable with a combination of a  
15 TNF $\alpha$  inhibitor and a RANK inhibitor include breast cancer, lung cancer, melanoma, bone cancer, squamous cell carcinoma, head and neck cancer, renal cancer, prostate cancer and cancers associated with hypercalcemia.

Nerve growth factors also can be combined with TNF $\alpha$  inhibitors to treat certain conditions. Such conditions include neurodegenerative diseases, spinal cord injury and multiple  
20 sclerosis. Other conditions treatable with this combination are glaucoma and diabetes.

In addition, the subject invention provides methods for treating a human patient in need thereof, the method involving administering to the patient a therapeutically effective amount of a TNF $\alpha$  inhibitor and an IL-4 inhibitor. IL-4 can induce an inflammatory effect in some instances, such as in asthma, a condition in which over-expression of IL-4 in the lungs causes epithelial cell  
25 hypertrophy and an accumulation of lymphocytes, eosinophils and neutrophils. This response is representative of the main features of the proinflammatory response induced by other Th2 cytokines. TNF $\alpha$  induces the proliferation of activated T cells and also plays a role in many diseases where IL-4 has a proinflammatory effect. In such diseases, the infiltration and proliferation of Th2 cells is fueled by TNF $\alpha$ , which cells in turn overproduce IL-4. In such  
30 settings, the suppression of both IL-4 and TNF $\alpha$  will have a greater impact on the disease than treatment that suppresses only one of these cytokines.

Combinations of TNF $\alpha$  inhibitors and IL-4 inhibitors preferably are administered one or more times per week. A preferred mode of administration is subcutaneous injection. Suitable dose ranges for IL-4 antagonists include doses of from about 1 ng/kg/day to about 10 mg/kg/day,  
35 more preferably from about 500 ng/kg/day to about 5 mg/kg/day, and most preferably from about 5  $\mu$ g/kg/day to about 2 mg/kg/day, administered to adults one time per week, two times per week, or three or more times per week. If injected, suitable doses may range from 1-20 mg/m<sup>2</sup>, and preferably is about 5-12 mg/m<sup>2</sup>. Alternatively, a flat dose of about 5-100 mg/dose may be used,

5 preferably about 20-30 mg per dose. For pediatric patients (age 4-17), one suitable regimen involves subcutaneous injection of 0.4 mg/kg, up to a maximum dose of 25 mg of IL-4R, administered two or three times per week. Another embodiment is directed to aerosol pulmonary administration, for example by nebulizer, which optimally will deliver a dose of 3 or more mg of a soluble IL-4R, and is taken at least once a week. Aerosolized IL-4R may be administered orally or nasally. One illustrative embodiment involves subcutaneous injection of a soluble human IL-10 4R once a week, at a dose of 1.5 to 3 mg. Doses will be adjusted as needed by the patient's physician in accord with standard medical practices.

Conditions effectively treated by a combination of a TNF $\alpha$  inhibitor and an IL-4 inhibitor include conditions in which a Th2-type immune response plays a role or conditions in which IL-4 15 plays a role in the inflammatory response. Lung disorders in which IL-4 plays a role include asthma, chronic obstructive pulmonary disease, pulmonary alveolar proteinosis, bleomycin-induced pneumopathy and fibrosis, radiation-induced pulmonary fibrosis, cystic fibrosis, collagen accumulation in the lungs, and ARDS, all of which may be treated with combinations of a TNF $\alpha$  inhibitor and an IL-4 inhibitor. Combinations of TNF $\alpha$  inhibitors and IL-4 inhibitors also are 20 useful for treating patients suffering from various skin disorders, including but not limited to dermatitis herpetiformis (Duhring's disease), atopic dermatitis, contact dermatitis, urticaria (including chronic idiopathic urticaria), and autoimmune blistering diseases, including pemphigus vulgaris and bullous pemphigoid. Other diseases treatable with the combination of a TNF $\alpha$  inhibitor and an IL-4 inhibitor include myasthenia gravis, sarcoidosis, including pulmonary 25 sarcoidosis, scleroderma, reactive arthritis, hyper IgE syndrome, multiple sclerosis and idiopathic hypereosinophil syndrome. The combination is used also for treating allergic reactions to medication and as an adjuvant to allergy immunotherapy. In addition, diseases that can be treated with a combination of a TNF $\alpha$  inhibitor and an IL-4 inhibitor may also be treated with an IL-4 inhibitor in the absence of a TNF $\alpha$  inhibitor.

30 IL-4 antagonist(s) may be included in compositions for in treating neurological disorders, such as diseases involving demyelination of nerves. Examples of such demyelinating diseases are multiple sclerosis, Miller-Fisher syndrome and Guillain-Barre syndrome. Multiple sclerosis (MS) is an autoimmune disease that attacks the central nervous system, and involves damage to the myelin sheath surrounding nerve cells. Guillain-Barre syndrome (GBS), also known as acute 35 febrile polyneuritis, involves demyelination of the peripheral nerves. GBS is mediated by an immune (inflammatory) response, and has been reported to follow infection or vaccination. Demyelinating diseases such as multiple sclerosis and Miller-Fisher syndrome are characterized by perivascular inflammation, and high levels of T cells and B cells that respond to myelin

5 antigens. Mast cells also are present at high levels in these disorders, and have been implicated in the detrimental autoimmune response in MS.

Provided herein are IL-4 antagonists for use in the treatment of additional neurologic disorders, including those involving inflammation of neural tissues, including nerves, brain or spinal cord. Such inflammation could result, for example, from a traumatic injury, herniated disc, 10 stroke, an aneurysm, a degenerative disorder or an autoimmune condition. Administration of an IL-4 antagonist may benefit a patient with a neurological disorder, such as those discussed above, by suppressing IL-4-induced inflammation or by suppressing a TH2-type immune response. Methods for treating such patients in accordance with the present invention are not limited by a particular mechanism of action, however.

15 In one embodiment, an IL-4 antagonist is administered to bind IL-4 that is secreted by mast cells in an MS patient. IL-4-mediated immune responses, such as a TH2-type response or an IL-4-mediated inflammatory response, thus are suppressed.

Patients with a demyelinating disease may be pre-screened to identify those with elevated 20 IL-4 levels, or to identify those with an elevated TH2-type immune response, thereby identifying the patients who may benefit most from treatment with an IL-4 antagonist or with a combination of an IL-4 antagonist plus an TNF $\alpha$  antagonist. Thus, methods for treating patients with neurological disorders such as multiple sclerosis, Miller-Fisher syndrome, or Guillain-Barre syndrome optionally comprise a first step of measuring a patient's IL-4 level, followed by administering an IL-4 antagonist to a patient in which IL-4 levels are elevated. Alternatively or 25 additionally, the first step comprises determining whether a patient has an elevated TH2-type immune response. In particular disorders, the incidence of elevated IL-4 levels, and the balance between TH1-type and TH2-type immune responses, may vary according to such factors as the stage of the disease (e.g., whether the patient is suffering an acute form of the disease, is in relapse, or is in remission); the particular form of the disease (e.g., optico-spinal MS versus the 30 conventional "Western" form of MS); or the sex of the patient. See Horiuchi et al. (*J. Neurological Sciences*, 172:17-24, 2000) and Hohnoki et al. (*J. Neuroimmunology* 87:27-32, 1998). Known techniques may be employed for measuring IL-4 levels, e.g., in a patient's serum, and for assessing TH2-type immune responses. Cytokine levels in blood samples may be measured by ELISA, for example.

35 IL-4 antagonists that may be employed in preparing compositions for use as described herein include, but are not limited to, IL-4 receptors (IL-4R) and other IL-4-binding molecules, IL-4 muteins and antibodies that bind specifically with IL-4 or IL-4 receptors thereby blocking signal transduction, as well as antisense oligonucleotides and ribozymes targeted to IL-4 or

5 IL-4R. Antibodies specific for IL-4 or IL-4 receptor may be prepared using standard procedures. Among the IL-4 receptors suitable for use as described herein are soluble fragments of human IL-4R that retain the ability to bind IL-4. Such fragments are capable of binding IL-4, and retain all or part of the IL-4R extracellular region.

10 A nucleotide sequence encoding human IL-4 receptor is shown in SEQ ID NO:1, and amino acid sequence for human IL-4 receptor is shown in SEQ ID NO:2. In a preferred embodiment, the IL-4 antagonist to be combined with a TNF $\alpha$  receptor is a soluble human IL-4 receptor comprising amino acids 1 to 207 of SEQ ID NO:2 and in another preferred embodiment, the IL-4 antagonist comprises amino acids -2 to 207 of SEQ ID NO:2.

15 After binding to an IL-4 antagonist according to the invention, endogenous IL-4 or IL-4R is thereby hindered or prevented from binding its natural receptor on cell surfaces *in vivo*, and thus IL-4-mediated biological activities are inhibited. IL-4 antagonists useful for the hereindescribed methods of treatment include molecules that selectively block the synthesis of endogenous IL-4 or IL-4R. IL-4 receptors are described in U.S. Patent 5,599,905; Idzerda et al., *J. Exp. Med.* 171:861-873, March 1990 (human IL-4R); and Mosley et al., *Cell* 59:335-348, 1989 (murine IL-4R), each of which is hereby incorporated by reference in its entirety. The protein described in those three references is sometimes referred to in the scientific literature as IL-4R $\alpha$ .  
20 Unless otherwise specified, the terms "IL-4R" and "IL-4 receptor" as used herein encompass this protein in various forms that are capable of functioning as IL-4 antagonists, including but not limited to soluble fragments, fusion proteins, oligomers, and variants that are capable of binding IL-4, as described in more detail below. Suitable IL-4Rs include variants in which valine replaces isoleucine at position 50 (see Idzerda et al., 1990), and include slow-release formulations, and PEGylated derivatives (modified with polyethylene glycol) are contemplated, as well as recombinant fusion proteins comprising heterologous polypeptides fused to the N-terminus or C-terminus of an IL-4R polypeptide, including signal peptides, immunoglobulin Fc regions, poly-His tags or the FLAG<sup>®</sup> polypeptide described in Hopp et al., *BioTechnology* 6:1204, 1988, and U.S. Patent 5,011,912, as well as fusions of IL-4 receptors with oligomer-promoting leucine zipper moieties. Soluble recombinant fusion proteins comprising an IL-4R and immunoglobulin constant regions are described, for example, in EP 464,533.  
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35 Various IL-4 antagonists that may be used for the hereindescribed methods of treatment can be identified, for example, by their ability to inhibit  $^3$ H-thymidine incorporation in cells that normally proliferate in response to IL-4, or by their ability to inhibit binding of IL-4 to cells that express IL-4R. In one assay for detecting IL-4 antagonists, one measures the ability of a putative antagonist to block the IL-4-induced enhancement of the expression of CD23 on the surfaces of

5 human B cells. For example, B cells isolated from human peripheral blood are incubated in microtiter wells in the presence of IL-4 and the putative antagonist. Following the incubation, washed cells are then incubated with labelled monoclonal antibody against CD23 (available from Pharmingen) to determine the level of CD23 expression. An anti-huIL-4R murine mAb (R&D Systems), previously shown to block the binding and function of both hIL-4 and hIL-13, may  
10 used as a positive control for neutralization of CD23 induction by IL-4. Alternatively, suitable IL-4 antagonists may be identified by determining their ability to prevent or reduce the impaired barrier function of epithelium that results when IL-4 is incubated with the epithelium. For this purpose, one may use confluent monolayers of human epithelial cell lines such as Calu-3 (lung) or T84 (intestinal epithelium). Incubation of such monolayers with IL-4 causes significant  
15 damage to their barrier function within about 48 hours. To assay IL-4 antagonists, monolayers may be tested for their permeability, for example, by adding radiolabeled mannitol to cells incubated with IL-4 in the presence or absence of an antagonist. Alternatively, transepithelial resistance (indicating an intact barrier) may be determined using a voltmeter.

20 The present invention also relates to the use of the disclosed TNF $\alpha$  inhibitors, such as TNFR:Fc, in the manufacture of a medicament for the prevention or therapeutic treatment of each medical disorder disclosed herein.

25 The disclosed TNF $\alpha$  inhibitors, compositions and combination therapies described herein are useful in medicines for treating bacterial, viral or protozoal infections, and complications resulting therefrom. One such disease is *Mycoplasma pneumonia*. In addition, provided herein is the use of TNFR:Fc to treat AIDS and related conditions, such as AIDS dementia complex, AIDS associated wasting, lipodystrophy due to antiretroviral therapy; and Kaposi's sarcoma. Provided herein is the use of TNFR:Fc for treating protozoal diseases, including malaria (including cerebral malaria) and schistosomiasis. Additionally provided is the use of TNFR:Fc to treat erythema nodosum leprosum; bacterial or viral meningitis; tuberculosis, including pulmonary  
30 tuberculosis; and pneumonitis secondary to a bacterial or viral infection. Provided also herein is the use of TNFR:Fc to prepare medicaments for treating louse-borne relapsing fevers, such as that caused by *Borrelia recurrentis*. TNFR:Fc can also be used to prepare a medicament for treating conditions caused by *Herpes* viruses, such as herpetic stromal keratitis, corneal lesions, and virus-induced corneal disorders. In addition, TNFR:Fc can be used in treating human papillomavirus  
35 infections, as well as in treating infectious mononucleosis. TNFR:Fc is used also to prepare medicaments to treat influenza, as well as to treat critical illness polyneuropathy and myopathy (CIPNM), an inflammatory syndrome that occasionally occurs in conjunction with prolonged

5 septic illnesses. The subject TNF $\alpha$  inhibitors are used also to treat transmissible spongiform encephalopathies, which is believed to be mediated by prions.

Another disorder that can be treated with any of the disclosed TNF $\alpha$  inhibitors, pharmaceutical compositions or combination therapies is tropical spastic paraparesis/HTLV-1 associated myelopathy (TSP/HAM). This disease is caused by infection with the human retrovirus HTLV-1. Recent studies have suggested that TNF $\alpha$  may play a role in the decreased glutamate uptake exhibited by HTLV-infected cells (Szymocha et al., *J Virol* 74:6433-41 (2000)). TSP/HAM is a slowly progressing condition of the spinal cord that causes weakness and muscle stiffness in the legs, often accompanied by a loss of sensation in the feet. Known treatments for this condition include corticosteroids and plasmapheresis. TSP/HAM may be treated with any of 10 the TNF $\alpha$  inhibitors disclosed herein, any of which may be administered concurrently with a corticosteroid, plasmapheresis or both. An exemplary TNF $\alpha$  inhibitor for treating TSP/HAM is TNFR:Fc. Sufficiency of treatment is determined by monitoring the patient for improvement in 15 leg strength, or an arrest of the patient's deterioration or by any other means deemed appropriate by the patient's physician.

20 Cardiovascular disorders are treatable with the disclosed TNF $\alpha$  inhibitors, pharmaceutical compositions or combination therapies. Examples of cardiovascular disorders treatable with a TNF $\alpha$  antagonist, such as TNFR:Fc, include: aortic aneurisms; arteritis; vascular occlusion, including cerebral artery occlusion; complications of coronary by-pass surgery; ischemia/reperfusion injury; heart disease, including atherosclerotic heart disease, myocarditis, 25 including chronic autoimmune myocarditis and viral myocarditis; heart failure, including chronic heart failure (CHF), cachexia of heart failure; myocardial infarction; restenosis after heart surgery; silent myocardial ischemia; post-implantation complications of left ventricular assist devices; Raynaud's phenomena; thrombophlebitis; vasculitis, including Kawasaki's vasculitis; giant cell arteritis, Wegener's granulomatosis; and Schoenlein-Henoch purpura.

30 TNF $\alpha$  and IL-8 have been implicated as chemotactic factors in atherosclerotic abdominal aortic aneurysm (Szekanecz et al., *Pathobiol* 62:134-139 (1994)). Abdominal aortic aneurysm may be treated in human patients by administering a soluble TNFR, such as TNFR:Fc, which may be administered in combination with an inhibitor of IL-8, such treatment having the effect of 35 reducing the pathological neovascularization associated with this condition.

Studies have shown that metalloproteases are a key element in myocardial remodeling and fibrosis. Thus, inhibiting TNF $\alpha$  and the inflammatory response in conjunction with direct inhibition of metalloproteases will reduce, prevent or reverse disorders such as left ventricular pump dysfunction. This is accomplished by co-administering a TNF $\alpha$  antagonist, such as

5 TNFR:Fc or other antagonist, together with a metalloprotease inhibitor. Alternatively, treatment of left ventricular pump dysfunction may involve administering a TNF $\alpha$  antagonist without the concurrent use of a metalloprotease inhibitor.

A combination of a TNF $\alpha$  inhibitor and one or more other anti-angiogenesis factors may be used to treat solid tumors, thereby reducing the vascularization that nourishes the tumor tissue.

10 Suitable anti-angiogenic factors for such combination therapies include IL-8 inhibitors, angiostatin, endostatin, kringle 5, inhibitors of vascular endothelial growth factor (VEGF), angiopoietin-2 or other antagonists of angiopoietin-1, antagonists of platelet-activating factor and antagonists of basic fibroblast growth factor. Antibodies against vascular endothelial growth factor, such as the recombinant humanized anti-VEGF produced by Genentech, Inc., are useful  
15 for combination treatments with TNF $\alpha$  inhibitors such as TNFR:Fc.

In addition, the subject TNF $\alpha$  inhibitors, compositions and combination therapies are used to treat chronic pain conditions, such as chronic pelvic pain, including chronic prostatitis/pelvic pain syndrome. As a further example, TNFR:Fc and the compositions and combination therapies of the invention are used to treat post-herpetic pain.

20 Provided also are methods for using TNF $\alpha$  inhibitors, compositions or combination therapies to treat various disorders of the endocrine system. For example, the TNF $\alpha$  inhibitors are used to treat juvenile onset diabetes (includes autoimmune and insulin-dependent types of diabetes) and also to treat maturity onset diabetes (includes non-insulin dependent and obesity-mediated diabetes). In addition, the subject compounds, compositions and combination therapies  
25 are used to treat secondary conditions associated with diabetes, such as diabetic retinopathy, kidney transplant rejection in diabetic patients, obesity-mediated insulin resistance, and renal failure, which itself may be associated with proteinuria and hypertension. Other endocrine disorders also are treatable with these compounds, compositions or combination therapies, including polycystic ovarian disease, X-linked adrenoleukodystrophy, hypothyroidism and  
30 thyroiditis, including Hashimoto's thyroiditis (i.e., autoimmune thyroiditis).

Conditions of the gastrointestinal system also are treatable with TNF $\alpha$  inhibitors, compositions or combination therapies, including coeliac disease. In addition, the compounds, compositions and combination therapies of the invention are used to treat Crohn's disease; nausea associated with gastrointestinal disorders or other systemic disorders; ulcerative colitis; idiopathic  
35 gastroparesis; cholelithiasis (gallstones); pancreatitis, including chronic pancreatitis and lung injury associated with acute pancreatitis; and ulcers, including gastric and duodenal ulcers.

Included also are methods for using the subject TNF $\alpha$  inhibitors, compositions or combination therapies for treating disorders of the genitourinary system, such as

5 glomerulonephritis, including autoimmune glomerulonephritis, glomerulonephritis due to exposure to toxins or glomerulonephritis secondary to infections with haemolytic streptococci or other infectious agents. Also treatable with the compounds, compositions and combination therapies of the invention are uremic syndrome and its clinical complications (for example, renal failure, anemia, and hypertrophic cardiomyopathy), including uremic syndrome associated with

10 exposure to environmental toxins, drugs or other causes. Further conditions treatable with the compounds, compositions and combination therapies of the invention are complications of hemodialysis; prostate conditions, including benign prostatic hypertrophy, nonbacterial prostatitis and chronic prostatitis; and complications of hemodialysis.

Also provided herein are methods for using TNF $\alpha$  inhibitors, compositions or combination therapies to treat various hematologic and oncologic disorders. For example, TNFR:Fc is used to treat various forms of cancer, including acute myelogenous leukemia, Epstein-Barr virus-positive nasopharyngeal carcinoma, gall bladder carcinoma, glioma, colon, stomach, prostate, renal cell, cervical and ovarian cancers, lung cancer (SCLC and NSCLC), including cancer-associated nausea, cancer-associated cachexia, fatigue, asthenia, paraneoplastic syndrome of cachexia and hypercalcemia. Additional diseases treatable with the subject TNF $\alpha$  inhibitors, compositions or combination therapies are solid tumors, including sarcoma, osteosarcoma, and carcinoma, such as adenocarcinoma (for example, breast cancer) and squamous cell carcinoma. In addition, the subject compounds, compositions or combination therapies are useful for treating leukemia, including acute myelogenous leukemia, chronic or acute lymphoblastic leukemia and hairy cell leukemia. Other malignancies with invasive metastatic potential can be treated with the subject compounds, compositions and combination therapies, including multiple myeloma. When TNF $\alpha$  inhibitors are used to treat a tumor, this treatment may be administered in combination with antibodies targeted to membrane proteins that are expressed at a high level on the particular tumor being treated. For example, tumors such as breast, ovarian and prostate carcinomas or other Her2-positive tumors, can be administered with TNFR:Fc or other TNF $\alpha$  inhibitors in combination with antibodies against Her2/neu, such as HERCEPTIN<sup>®</sup> (Genentech, Inc.).

In addition, the disclosed TNF $\alpha$  inhibitors, compositions and combination therapies can be used to treat anemias and hematologic disorders, including anemia of chronic disease, aplastic anemia, including Fanconi's aplastic anemia; idiopathic thrombocytopenic purpura (ITP); myelodysplastic syndromes (including refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation); myelofibrosis/myeloid metaplasia; and sickle cell vasocclusive crisis. In

5 addition, TNF $\alpha$  inhibitors, such as TNFR:Fc, are useful for treating chronic idiopathic neutropenia.

Undesired side effects of certain therapies can be treated with TNF $\alpha$  antagonists, such as TNFR:Fc. Such therapies are those mediated by elevated TNF $\alpha$  levels. For example, TNF $\alpha$  antagonists may be administered to help combat the nausea associated with chemotherapy or 10 other drug-induced nausea. In addition, TNF $\alpha$  antagonists are used to treat the radiation-induced brain damage associated with radiation treatment for brain tumors. Furthermore, TNF $\alpha$  antagonists are used to treat the toxicity associated with the administration of monoclonal antibodies directed against antigens present on the surface of particular kinds of cancer cells.

Various lymphoproliferative disorders also are treatable with the disclosed TNF $\alpha$  15 inhibitors, compositions or combination therapies. These include, but are not limited to autoimmune lymphoproliferative syndrome (ALPS), chronic lymphoblastic leukemia, hairy cell leukemia, chronic lymphatic leukemia, peripheral T-cell lymphoma, small lymphocytic lymphoma, mantle cell lymphoma, follicular lymphoma, Burkitt's lymphoma, Epstein-Barr virus-positive T cell lymphoma, histiocytic lymphoma, Hodgkin's disease, diffuse aggressive 20 lymphoma, acute lymphatic leukemias, T gamma lymphoproliferative disease, cutaneous B cell lymphoma, cutaneous T cell lymphoma (i.e., mycosis fungoides) and Sézary syndrome.

In addition, the subject TNF $\alpha$  inhibitors, compositions and combination therapies are used to treat hereditary conditions such as Gaucher's disease, Huntington's disease, linear IgA disease, and muscular dystrophy.

25 Other conditions treatable by the disclosed TNF $\alpha$  inhibitors, compositions and combination therapies include those resulting from injuries to the head or spinal cord, and including subdural hematoma due to trauma to the head.

The disclosed TNF $\alpha$  inhibitors, compositions and combination therapies are further used to treat conditions of the liver such as hepatitis, including acute alcoholic hepatitis, acute drug- 30 induced or viral hepatitis, hepatitis A, B and C, sclerosing cholangitis and inflammation of the liver due to unknown causes.

In addition, the disclosed TNF $\alpha$  inhibitors, compositions and combination therapies are used to treat various disorders that involve hearing loss and that are associated with abnormal TNF $\alpha$  expression. One of these is inner ear or cochlear nerve-associated hearing loss that is 35 thought to result from an autoimmune process, i.e., autoimmune hearing loss. This condition currently is treated with steroids, methotrexate and/or cyclophosphamide, which may be administered concurrently with the TNFR:Fc or other TNF $\alpha$  inhibitor. Also treatable with the

5 disclosed TNF $\alpha$  inhibitors, compositions and combination therapies is cholesteatoma, a middle ear disorder often associated with hearing loss.

In addition, the subject invention provides TNF $\alpha$  inhibitors, compositions and combination therapies for the treatment of non-arthritic medical conditions of the bones and joints. This encompasses osteoclast disorders that lead to bone loss, such as but not limited to 10 osteoporosis, including post-menopausal osteoporosis, periodontitis resulting in tooth loosening or loss, and prosthesis loosening after joint replacement (generally associated with an inflammatory response to wear debris). This latter condition also is called "orthopedic implant osteolysis." Other conditions treatable by administering TNFR $\alpha$  inhibitors, such as TNFR:Fc, include 15 temporal mandibular joint dysfunction (TMJ) and bone loss due to the hypercalcemia of cancer, including metastases to bone, such as, for example, may occur in melanoma or carcinoma of lung, breast, lung, squamous cell carcinoma, head and neck cancer, renal cancer, or prostate cancer.

A number of pulmonary disorders also can be treated with the disclosed TNF $\alpha$  inhibitors, compositions and combination therapies. One such condition is adult respiratory distress 20 syndrome (ARDS), which is associated with elevated TNF $\alpha$ , and may be triggered by a variety of causes, including exposure to toxic chemicals, pancreatitis, trauma or other causes. The disclosed compounds, compositions and combination therapies of the invention also are useful for treating broncho-pulmonary dysplasia (BPD); lymphangioleiomyomatosis; pulmonary hypertension; and 25 chronic fibrotic lung disease of preterm infants. In addition, the compounds, compositions and combination therapies of the invention are used to treat occupational lung diseases, including asbestosis, coal worker's pneumoconiosis, silicosis or similar conditions associated with long-term exposure to fine particles. In other aspects of the invention, the disclosed compounds, 30 compositions and combination therapies are used to treat pulmonary disorders, including chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis or emphysema; fibrotic lung diseases, such as cystic fibrosis, idiopathic pulmonary fibrosis and radiation-induced pulmonary fibrosis; sarcoidosis, including pulmonary sarcoidosis; and allergies, including allergic rhinitis, contact dermatitis, atopic dermatitis and asthma.

Cystic fibrosis is an inherited condition characterized primarily by the accumulation of 35 thick mucus, predisposing the patient to chronic lung infections and obstruction of the pancreas, which results in malabsorption of nutrients and malnutrition. TNFR:Fc may be administered to treat cystic fibrosis. If desired, treatment with TNFR:Fc may be administered concurrently with corticosteroids, mucus-thinning agents such as inhaled recombinant deoxyribonuclease I (such as PULMOZYME $^{\circledR}$ ; Genentech, Inc.) or inhaled tobramycin (TOBI $^{\circledR}$ ; Pathogenesis, Inc.). TNFR:Fc

5 also may be administered concurrently with corrective gene therapy, drugs that stimulate cystic fibrosis cells to secrete chloride or other yet-to-be-discovered treatments. Sufficiency of treatment may be assessed, for example, by observing a decrease in the number of pathogenic organisms in sputum or lung lavage (such as *Haemophilus influenzae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*), by monitoring the patient for weight gain, by detecting an  
10 increase in lung capacity or by any other convenient means.

15 TNFR:Fc or TNFR:Fc combined with the cytokine IFN $\gamma$ -1b (such as ACTIMMUNE<sup>®</sup>; InterMune Pharmaceuticals) may be used for treating cystic fibrosis or fibrotic lung diseases, such as idiopathic pulmonary fibrosis, radiation-induced pulmonary fibrosis and bleomycin-induced pulmonary fibrosis. In addition, this combination is useful for treating other diseases characterized by organ fibrosis, including systemic sclerosis (also called "scleroderma"), which often involves fibrosis of the liver. For treating cystic fibrosis, TNFR:Fc and IFN $\gamma$ -1b may be combined with PULMOZYME<sup>®</sup> or TOBI<sup>®</sup> or other treatments for cystic fibrosis.

20 TNFR:Fc alone or in combination with IFN $\gamma$ -1b may be administered together with other treatments presently used for treating fibrotic lung disease. Such additional treatments include glucocorticoids, azathioprine, cyclophosphamide, penicillamine, colchicine, supplemental oxygen and so forth. Patients with fibrotic lung disease, such as IPF, often present with nonproductive cough, progressive dyspnea, and show a restrictive ventilatory pattern in pulmonary function tests. Chest radiographs reveal fibrotic accumulations in the patient's lungs. When treating fibrotic lung disease in accord with the disclosed methods, sufficiency of treatment may be  
25 detected by observing a decrease in the patient's coughing (when cough is present), or by using standard lung function tests to detect improvements in total lung capacity, vital capacity, residual lung volume or by administering a arterial blood gas determination measuring desaturation under exercising conditions, and showing that the patient's lung function has improved according to one or more of these measures. In addition, patient improvement may be determined through chest  
30 radiography results showing that the progression of fibrosis in the patient's lungs has become arrested or reduced.

35 In addition, TNF inhibitors (including soluble TNFRs or antibodies against TNF $\alpha$  or TNFR) are useful for treating organ fibrosis when administered in combination with relaxin, a hormone that down-regulates collagen production thus inhibiting fibrosis, or when given in combination with agents that block the fibrogenic activity of TGF- $\beta$ . Combination therapies using TNFR:Fc and recombinant human relaxin are useful, for example, for treating systemic sclerosis or fibrotic lung diseases, including cystic fibrosis, idiopathic pulmonary fibrosis, radiation-induced pulmonary fibrosis and bleomycin-induced pulmonary fibrosis.

5 Other embodiments provide methods for using the disclosed TNF $\alpha$  inhibitors, compositions or combination therapies to treat a variety of rheumatic disorders. These include: adult and juvenile rheumatoid arthritis; systemic lupus erythematosus; gout; osteoarthritis; polymyalgia rheumatica; seronegative spondylarthropathies, including ankylosing spondylitis; and Reiter's disease (reactive arthritis). The subject TNF $\alpha$  inhibitors, compositions and combination therapies are used also to treat psoriatic arthritis and chronic Lyme arthritis. Also 10 treatable with these compounds, compositions and combination therapies are Still's disease and uveitis associated with rheumatoid arthritis. In addition, the compounds, compositions and combination therapies of the invention are used in treating disorders resulting in inflammation of the voluntary muscle, including dermatomyositis and polymyositis. Moreover, the compounds, 15 compositions and combinations disclosed herein are useful for treating sporadic inclusion body myositis, as TNF $\alpha$  may play a significant role in the progression of this muscle disease. In addition, the compounds, compositions and combinations disclosed herein are used to treat multicentric reticulohistiocytosis, a disease in which joint destruction and papular nodules of the face and hands are associated with excess production of preinflammatory cytokines by 20 multinucleated giant cells.

The TNF $\alpha$  inhibitors, compositions and combination therapies of the invention may be used to inhibit hypertrophic scarring, a phenomenon believed to result in part from excessive TNF $\alpha$  secretion. TNF inhibitors may be administered alone or concurrently with other agents that inhibit hypertrophic scarring, such as inhibitors of TGF- $\alpha$ .

25 Cervicogenic headache is a common form of headache arising from dysfunction in the neck area, and which is associated with elevated levels of TNF $\alpha$ , which are believed to mediate an inflammatory condition that contributes to the patient's discomfort (Martelletti, *Clin Exp Rheumatol* 18(2 Suppl 19):S33-8 (Mar-Apr, 2000)). Cervicogenic headache may be treated by administering an inhibitor of TNF $\alpha$  as disclosed herein, thereby reducing the inflammatory 30 response and associated headache pain.

The TNF $\alpha$  inhibitors, compositions and combination therapies of the invention are useful for treating primary amyloidosis. In addition, the secondary amyloidosis that is characteristic of various conditions also are treatable with TNF $\alpha$  inhibitors such as TNFR:Fc, and the compositions and combination therapies described herein. Such conditions include: Alzheimer's 35 disease, secondary reactive amyloidosis; Down's syndrome; and dialysis-associated amyloidosis. Also treatable with the compounds, compositions and combination therapies of the invention are inherited periodic fever syndromes, including familial Mediterranean fever,

5 hyperimmunoglobulin D and periodic fever syndrome and TNF-receptor associated periodic syndromes (TRAPS).

Disorders associated with transplantation also are treatable with the disclosed TNF $\alpha$  inhibitors, compositions or combination therapies, such as graft-versus-host disease, and complications resulting from solid organ transplantation, including transplantation of heart, liver, 10 lung, skin, kidney or other organs. TNF $\alpha$  inhibitors, such as TNFR:Fc or anti-TNF $\alpha$  antibodies are used also to treat or prevent corneal transplant rejection. Such inhibitors may be administered, for example, to prevent or inhibit the development of bronchiolitis obliterans, such as bronchiolitis obliterans after lung transplantation and bronchiolitis obliterans organizing pneumonia. Patients undergoing autologous hematopoietic stem cell transplantation in the form 15 of peripheral blood stem cell transplantation may develop "engraftment syndrome," or "ES," which is an adverse and generally self-limited response that occurs about the time of hematopoietic engraftment and which can result in pulmonary deterioration. ES may be treated with inhibitors of either IL-8 or TNF $\alpha$  (such as TNFR:Fc), or with a combination of inhibitors against both of these cytokines. The disclosed TNF $\alpha$  inhibitors also are useful for treating or 20 preventing graft failure, such as bone marrow graft rejection or failure of the recipient's body to accept other types of grafts, such as liver or other solid organ transplants, in which graft rejection is often accompanied by elevated levels of TNF $\alpha$  and IL-10. Graft rejection may be treated with a combination of a TNF $\alpha$  inhibitor and an IL-10 inhibitor.

Ocular disorders also are treatable with the disclosed TNF $\alpha$  inhibitors, compositions or 25 combination therapies, including rhegmatogenous retinal detachment, and inflammatory eye disease, and inflammatory eye disease associated with smoking as well as macular degeneration associated with smoking or associated with aging.

TNF $\alpha$  inhibitors such as TNFR:Fc and the disclosed compositions and combination therapies also are useful for treating disorders that affect the female reproductive system. 30 Examples include, but are not limited to, multiple implant failure/infertility; fetal loss syndrome or IV embryo loss (spontaneous abortion); preeclamptic pregnancies or eclampsia; and endometriosis.

In addition, the disclosed TNF $\alpha$  inhibitors, compositions and combination therapies are useful for treating obesity, including treatment to bring about a decrease in leptin formation, or 35 weight gain associated with the use of anti-depressant medications. Also, the compounds, compositions and combination therapies of the invention are used to treat neurogenic pain, sciatica, symptoms of aging, severe drug reactions (for example, IL-2 toxicity or bleomycin-induced pneumopathy and fibrosis), or to suppress the inflammatory response prior, during or

5 after the transfusion of allogeneic red blood cells in cardiac or other surgery, or in treating a traumatic injury to a limb or joint, such as traumatic knee injury. Various other medical disorders treatable with the disclosed TNF $\alpha$  inhibitors, compositions and combination therapies include; multiple sclerosis; Behcet's syndrome; Sjogren's syndrome; autoimmune hemolytic anemia; beta thalassemia; amyotrophic lateral sclerosis (Lou Gehrig's Disease); Parkinson's disease; and

10 tenosynovitis of unknown cause, as well as various autoimmune disorders or diseases associated with hereditary deficiencies.

The disclosed TNF $\alpha$  inhibitors, compositions and combination therapies furthermore are useful for treating acute polyneuropathy; anorexia nervosa; Bell's palsy; chronic fatigue syndrome; transmissible dementia, including Creutzfeld-Jacob disease; demyelinating

15 neuropathy; Guillain-Barre syndrome; vertebral disc disease; Gulf war syndrome; myasthenia gravis; silent cerebral ischemia; sleep disorders, including narcolepsy and sleep apnea; chronic neuronal degeneration; and stroke, including cerebral ischemic diseases.

Disorders involving the skin or mucous membranes also are treatable using the disclosed TNF $\alpha$  inhibitors, compositions or combination therapies. Such disorders include acantholytic diseases, including Darier's disease, keratosis follicularis and pemphigus vulgaris. Also treatable with the subject TNF $\alpha$  inhibitors, compositions and combination therapies are acne; acne rosacea; alopecia areata; aphthous stomatitis; bullous pemphigoid; burns; dermatitis herpetiformis; eczema; erythema, including erythema multiforme and erythema multiforme bullosum (Stevens-Johnson syndrome); inflammatory skin disease; lichen planus; linear IgA

20 bullous disease (chronic bullous dermatosis of childhood); loss of skin elasticity; mucosal surface ulcers; neutrophilic dermatitis (Sweet's syndrome); pityriasis rubra pilaris; psoriasis; pyoderma gangrenosum; and toxic epidermal necrolysis.

In one preferred embodiment, the therapeutic agent is a soluble TNF receptor, and preferably is a TNFR-Ig. In a preferred embodiment, the TNFR-Ig is TNFR:Fc, which may be

30 administered in the form of a pharmaceutically acceptable composition as described herein. The diseases described herein may be treated by administering TNFR:Fc one or more times per week by subcutaneous injection, although other routes of administration may be used if desired. In one exemplary regimen for treating adult human patients, 25 mg of TNFR:Fc is administered by subcutaneous injection two times per week or three times per week for one or more weeks, and

35 preferably for four or more weeks. Alternatively, a dose of 5-12 mg/m<sup>2</sup> or a flat dose of 50 mg is injected subcutaneously one time or two times per week for one or more weeks. In other embodiments, psoriasis is treated with TNFR:Fc in a sustained-release form, such as TNFR:Fc that is encapsulated in a biocompatible polymer, TNFR:Fc that is admixed with a biocompatible

5 polymer (such as topically applied hydrogels), and TNFR:Fc that is encased in a semi-permeable implant.

Various other medicaments used to treat the diseases described herein may also be administered concurrently with compositions comprising TNF $\alpha$  inhibitors, such as TNFR:Fc. Such medicaments include: NSAIDs; DMARDs; analgesics; topical steroids; systemic steroids 10 (e.g., prednisone); cytokines; antagonists of inflammatory cytokines; antibodies against T cell surface proteins; oral retinoids; salicylic acid; and hydroxyurea. Suitable analgesics for such combinations include: acetaminophen, codeine, propoxyphene napsylate, oxycodone hydrochloride, hydrocodone bitartrate and tramadol. DMARDs suitable for such combinations include: azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine sulfate, 15 methotrexate, leflunomide, minocycline, penicillamine, sulfasalazine, oral gold, gold sodium thiomalate and aurothioglucose. In addition, the TNFR:Fc or other TNFR mimic may be administered in combination with antimalarials or colchicine. NSAIDs suitable for the subject combination treatments include: salicylic acid (aspirin) and salicylate derivatives; ibuprofen; indomethacin; celecoxib (CELEBREX $\circledR$ ); rofecoxib (VIOXX $\circledR$ ); ketorolac; nambumetone; 20 piroxicam; naproxen; oxaprozin; sulindac; ketoprofen; diclofenac; and other COX-1 and COX-2 inhibitors, propionic acid derivatives, acetic acid derivatives, fumaric acid derivatives, carboxylic acid derivatives, butyric acid derivatives, oxicams, pyrazoles and pyrazolones, including newly developed anti-inflammatories.

If an antagonist against an inflammatory cytokine is administered concurrently with 25 TNFR:Fc, suitable targets for such antagonists include TGF $\beta$ , IL-6 and IL-8.

In addition, TNFR:Fc may be used in combination with topical steroids, systemic steroids, antagonists of inflammatory cytokines, antibodies against T cell surface proteins, methotrexate, cyclosporine, hydroxyurea and sulfasalazine.

In addition to human patients, inhibitors of TNF $\alpha$  are useful in the treatment of 30 autoimmune and inflammatory conditions in non-human animals, such as pets (dogs, cats, birds, primates, etc.), domestic farm animals (horses cattle, sheep, pigs, birds, etc.), or any animal that suffers from a TNF $\alpha$ -mediated inflammatory or arthritic condition comparable to one of the conditions described herein. In such instances, an appropriate dose may be determined according to the animal's body weight. For example, a dose of 0.2-1 mg/kg may be used. Alternatively, the 35 dose is determined according to the animal's surface area, an exemplary dose ranging from 0.1-20 mg/m $^2$ , or more preferably, from 5-12 mg/m $^2$ . For small animals, such as dogs or cats, a suitable dose is 0.4 mg/kg. In a preferred embodiment, TNFR:Fc (preferably constructed from genes derived from the same species as the patient), or another soluble TNFR mimic, is

- 5 administered by injection or other suitable route one or more times per week until the animal's condition is improved, or it may be administered indefinitely.

What is claimed is:

1. A method of treating a human patient in need thereof comprising administering to said patient a therapeutically effective amount of a TNF $\alpha$  inhibitor and an IL-4 inhibitor.
2. The method of Claim 1, wherein the TNF $\alpha$  inhibitor is a soluble TNF $\alpha$  receptor and the IL-4 inhibitor comprises a soluble IL-4 receptor or an antibody that specifically binds human IL-4.
3. The method of Claim 2, wherein the soluble TNF $\alpha$  receptor and the IL-4 inhibitor are administered one or more times per week.
4. The method of Claim 2, wherein the IL-4 inhibitor is a soluble IL-4 receptor and the soluble TNF $\alpha$  receptor is TNFR:Fc and the soluble IL-4 receptor and the TNFR:Fc are administered by subcutaneous injection.
5. The method of Claim 2, wherein the IL-4 inhibitor is a soluble IL-4 receptor and the soluble IL-4 receptor is administered by aerosol inhalation.
6. The method of Claim 4, wherein the patient is an adult and the soluble TNF receptor is TNFR:Fc that is injected in the amount of 5-12 mg/m<sup>2</sup>, 25 mg or 50 mg.
7. The method of Claim 1, wherein the patient suffers from a disorder selected from the group consisting of a lung disorder and a skin disorder,
8. The method of Claim 7, wherein the patient suffers from a lung disorder that is selected from the group consisting of asthma, chronic obstructive pulmonary disease, pulmonary alveolar proteinosis, bleomycin-induced pneumopathy and fibrosis, radiation-induced pulmonary fibrosis, cystic fibrosis, collagen accumulation in the lungs and ARDS.
9. The method of Claim 7, wherein the patient suffers from a skin disorder that is selected from the group consisting of dermatitis herpetiformis, atopic dermatitis, contact dermatitis, urticaria, and an autoimmune blistering disease.

10. The method of Claim 1, wherein the patient is undergoing immunotherapy for allergies or suffers from a disorder that is selected from the group consisting of myasthenia gravis, sarcoidosis, scleroderma, reactive arthritis, hyper IgE syndrome, multiple sclerosis, idiopathic hypereosinophil syndrome and an allergic reaction to medication.

11. A method according to any of Claims 1-5 or 7-10, wherein the patient is a pediatric patient and the TNF $\alpha$  inhibitor is TNFR:Fc, and further wherein the TNFR:Fc is administered by subcutaneous injection one or more times per week at a dose of 0.4 mg/kg, up to a maximum of 25 mg.

12. A method according to any of Claims 1-11, wherein the IL-4 inhibitor is a soluble IL-4 receptor that is administered at least one time per week by subcutaneous injection at a dose of 1-20 mg/m<sup>2</sup> or at a flat dose of 5-100 mg/dose or is administered by nebulizer at a dose of at least 3 mg.

13. A method of treating a human patient suffering from a neurological disorder comprising administering to said patient a therapeutically effective amount of an IL-4 inhibitor.

14. A method according to Claim 13 wherein the neurological disorder is a demyelinating disease or is a disorder involving inflammation of nerves, brain or spinal cord.

15. A method according to Claim 14, wherein the disorder is a demyelinating disease selected from the group consisting of multiple sclerosis, Miller-Fisher syndrome and Guillain-Barre syndrome.

16. A method according to any of Claims 1-15, wherein the IL-4 inhibitor is a soluble IL-4 receptor comprising amino acids 1 to 207 of SEQ ID NO:2.

17. A method according to any of Claims 1-15, wherein the IL-4 inhibitor is a soluble IL-4 receptor comprising amino acids -2 to 207 of SEQ ID NO:2.

## SEQUENCE LISTING

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 Glu Glu Asn Gly Gly Phe Cys Gln Gln Asp Met Gly Glu Ser Cys Leu  
 395 400 405  
 Leu Pro Pro Ser Gly Ser Thr Ser Ala His Met Pro Trp Asp Glu Phe  
 410 415 420  
 Pro Ser Ala Gly Pro Lys Glu Ala Pro Pro Trp Gly Lys Glu Gln Pro  
 425 430 435  
 Leu His Leu Glu Pro Ser Pro Pro Ala Ser Pro Thr Gln Ser Pro Asp  
 440 445 450 455  
 Asn Leu Thr Cys Thr Glu Thr Pro Leu Val Ile Ala Gly Asn Pro Ala  
 460 465 470  
 Tyr Arg Ser Phe Ser Asn Ser Leu Ser Gln Ser Pro Cys Pro Arg Glu  
 475 480 485  
 Leu Gly Pro Asp Pro Leu Leu Ala Arg His Leu Glu Val Glu Pro  
 490 495 500  
 Glu Met Pro Cys Val Pro Gln Leu Ser Glu Pro Thr Thr Val Pro Gln  
 505 510 515  
 Pro Glu Pro Glu Thr Trp Glu Gln Ile Leu Arg Arg Asn Val Leu Gln  
 520 525 530 535  
 His Gly Ala Ala Ala Ala Pro Val Ser Ala Pro Thr Ser Gly Tyr Gln  
 540 545 550  
 Glu Phe Val His Ala Val Glu Gln Gly Gly Thr Gln Ala Ser Ala Val  
 555 560 565  
 Val Gly Leu Gly Pro Pro Gly Glu Ala Gly Tyr Lys Ala Phe Ser Ser  
 570 575 580

Leu Leu Ala Ser Ser Ala Val Ser Pro Glu Lys Cys Gly Phe Gly Ala  
585 590 595

Ser Ser Gly Glu Glu Gly Tyr Lys Pro Phe Gln Asp Leu Ile Pro Gly  
600 605 610 615

Cys Pro Gly Asp Pro Ala Pro Val Pro Val Pro Leu Phe Thr Phe Gly  
620 625 630

Leu Asp Arg Glu Pro Pro Arg Ser Pro Gln Ser Ser His Leu Pro Ser  
635 640 645

Ser Ser Pro Glu His Leu Gly Leu Glu Pro Gly Glu Lys Val Glu Asp  
650 655 660

Met Pro Lys Pro Pro Leu Pro Gln Glu Gln Ala Thr Asp Pro Leu Val  
665 670 675

Asp Ser Leu Gly Ser Gly Ile Val Tyr Ser Ala Leu Thr Cys His Leu  
680 685 690 695

Cys Gly His Leu Lys Gln Cys His Gly Gln Glu Asp Gly Gly Gln Thr  
700 705 710

Pro Val Met Ala Ser Pro Cys Cys Gly Cys Cys Cys Gly Asp Arg Ser  
715 720 725

Ser Pro Pro Thr Thr Pro Leu Arg Ala Pro Asp Pro Ser Pro Gly Gly  
730 735 740

Val Pro Leu Glu Ala Ser Leu Cys Pro Ala Ser Leu Ala Pro Ser Gly  
745 750 755

Ile Ser Glu Lys Ser Lys Ser Ser Ser Phe His Pro Ala Pro Gly  
760 765 770 775

Asn Ala Gln Ser Ser Ser Gln Thr Pro Lys Ile Val Asn Phe Val Ser  
780 785 790

Val Gly Pro Thr Tyr Met Arg Val Ser  
795 800



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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

**WO 01/62272 A3**

(54) Title: SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR AND IL-4 INHIBITOR FOR THE TREATMENT OF MEDICAL DISORDERS

(57) Abstract: The invention pertains to methods and compositions for treating medical disorders characterized by elevated levels or abnormal expression of TNF $\alpha$  by administering a TNF $\alpha$  inhibitor, such as recombinant TNFR:Fc, and to combination treatments involving the administration of a TNF $\alpha$  inhibitor and an IL-4 inhibitor. Also provided are methods and compositions involving IL-4 inhibitors for use in treating neurological disorders.

# INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/US 01/06037

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 A61K38/17 A61K39/395 A61P11/00 A61P17/00 A61P25/00  
A61P37/00 // (A61K39/395, 38:17)

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, SEQUENCE SEARCH, WPI Data, PAJ, BIOSIS, MEDLINE, CHEM ABS Data, EMBASE, SCISEARCH

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 958 820 A (SANOFI SYNTHELABO) 24 November 1999 (1999-11-24) page 3, line 41 - line 45 page 5, line 35 - line 43 claims 1-5 ----	1,7-10, 13-15
X	WO 96 04388 A (BROWNE MICHAEL JOSEPH ;CHAPMAN CONRAD GERALD (GB); CLINKENBEARD HE) 15 February 1996 (1996-02-15) page 1, line 10 - line 18 page 7, line 20 -page 8, line 2 page 8, line 36 -page 9, line 6 claims 1,15-19 ----	13-15
Y	----- -/-	16,17



Further documents are listed in the continuation of box C



Patent family members are listed in annex

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

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Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/06037

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 767 065 A (BECKMANN M PATRICIA ET AL) 16 June 1998 (1998-06-16)	16,17
A	column 3, line 11 - line 32 claims 1-8,11-14,16,17,19-21 column 4, line 67 -column 5, line 4 column 5, line 24 - line 27 column 5, line 46 - line 66 column 6, line 54 - line 67 column 10, line 25 - line 43 column 15, line 51 -column 16, line 65 ---	1-12
A	MEASE P ET AL: "ENBREL (ETANERCEFT) IN PATIENTS WITH PSORIATIC ARTHRITIS AND PSORIASIS" ARTHRITIS AND RHEUMATISM, LIPPINCOTT, PHILADELPHIA, US, vol. 42, no. 9, 1999, page S377 XP000960436 ISSN: 0004-3591 the whole document ---	1-7,11
A	WO 97 41895 A (HOFFMANN LA ROCHE) 13 November 1997 (1997-11-13) the whole document -----	1-8,11

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,3,7-17 (all partially)

Present claims 1,7-10,12,16,17 relate to a compound defined by reference to a desirable characteristic or property, namely its inhibitory effect on TNF alpha. Additionally present claims 1,3,7-11,13-15 relate to a compound only characterized by its inhibitory effect on IL-4. These claims do not contain any structural or essential characteristics neither of the TNF alpha inhibitor nor the IL-4 inhibitor.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in the description at page 6 line 31, page 7 lines 19-24, page 15 lines 9-13 and in claims 2, 4-6, 16 and 17. Furthermore the general terms TNF alpha inhibitor and IL-4 inhibitor have been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No

PCT/US 01/06037

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